

107* Effect of multiple courses of Aztreonam Lysine for Inhalation (AZLI) on FEV1 and weight in patients with cystic fibrosis (CF) and *Pseudomonas aeruginosa* (PA): Analysis of 18 month data from CP-AI-006

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Rationale: The primary cause of morbidity and mortality in CF is progressive lung disease associated with PA infection. New inhaled anti-PA antibiotics are needed to slow lung disease progression.

Methods: This open label trial included patients with CF and PA who previously participated in one of two double blind, placebo controlled trials. In this study, patients (N=274; mean age 28.5 years; range 8 to 74) received 75 mg AZLI, a novel formulation of aztreonam, using the PARI eFlow[®] Electronic Nebuliser (BID or TID) for up to nine courses (28 days on therapy, followed by 28 days off) over 18 months. Concomitant routine CF therapies were allowed. Efficacy endpoints included change in pulmonary function (FEV1) and weight.

Results: All patients have completed study participation; median time on study was 507 days. Mean percent change in weight from baseline (Visit 1) to end of course 9 was 3.24% for BID and 3.57% for TID. Mean percent change in FEV1 from baseline to end of course 9 was 1.3% for BID and 4.0% for TID. Mean changes in FEV1 from baseline were positive after all nine courses for BID and TID.

Conclusions: Patients experienced improvements (compared to study baseline) in FEV1 and weight after 9 courses with either AZLI BID or TID, but TID results were consistently superior. Repeated treatment with AZLI is effective in improving lung function and weight (on average) in CF patients with moderate to severe lung disease.

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109 Adherence over multiple courses of Aztreonam Lysine for Inhalation (AZLI): effect on disease-related endpoints in patients with cystic fibrosis (CF) and *Pseudomonas aeruginosa* (PA)

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Rationale: New inhaled anti-PA antibiotics are needed to slow progression of lung disease in CF. Adherence to inhaled therapies is crucial to ensure treatment benefit.

Methods: This ongoing open label trial enrolled 274 patients who previously participated in one of two phase 3 trials (AIR-CF1/2). Patients received 75 mg AZLI (BID or TID) in up to nine courses (28 days on/28 days off therapy) over 18 months using the PARI eFlow[®] Electronic Nebulizer (2–3 minute dosing time). Relative adherence (RA) was calculated as vials used as a percentage of the number prescribed. A patient was considered adherent if RA \geq 80%. Average within course change from baseline (over first 3 cycles) in FEV1% predicted and respiratory symptoms (CFQ-R) was evaluated for patients originating from AIR-CF2 (randomized comparison of BID and TID). Results for the first 6 AZLI cycles are also presented.

Results: Mean RA was \geq 94% with \geq 89% of patients compliant for each of the first 3 AZLI cycles, with no difference between regimens. Degree of adherence is supported by the observed dose response. Over the first 3 courses, FEV1% predicted and CFQ-R improvements were greater for TID compared to BID (7.0% vs 4.2%, $p=0.01$; 5.9 vs 1.9, $p=0.04$, respectively).

Conclusions: Adherence to BID and TID AZLI therapy was high and maintained for multiple cycles. BID dosing was beneficial, but TID results were consistently better. Repeated treatment with AZLI is effective in CF patients with moderate to severe lung disease.

108 Efficacy of Aztreonam Lysine for Inhalation (AZLI) in patients with cystic fibrosis and drug resistant *P. aeruginosa* (DRPA)

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Background: Identification of DRPA has increased and is associated with accelerated progression of lung disease caused by chronic airway infection. AZLI is an inhaled antibiotic in development for patients with CF. The clinical efficacy of a 28-day course of AZLI in patients with DRPA identified before treatment has been evaluated in two Phase 3 double-blind, multicenter, randomized, placebo-controlled studies. In study AIR-CF1, patients received AZLI following a minimum 28-day period without antipseudomonal antibiotics. In AIR-CF2, patients received AZLI immediately after a 28-day course of tobramycin inhalation solution.

Results: Patients treated with 75 mg AZLI TID demonstrated improvements in respiratory symptoms, pulmonary function, and sputum PA density, regardless of whether DRPA was present. In addition, susceptibility data at the end of the treatment course suggest that AZLI increases tobramycin susceptibility of PA isolates and does not induce antibiotic resistance.

Conclusion: The increasing presence of DRPA has created an unmet therapeutic need for new inhaled antibiotic options. AZLI TID appears to be active against DRPA and thus addresses this need.

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Clinical efficacy outcomes in AIR-CF1//AIR-CF2

	N	Mean Change in: CFQ-R Respiratory Symptoms Score	Percent FEV1 (L)	log ₁₀ Sputum PA CFU density
Placebo				
No DRPA*	33/24	-1.30/0.48	-0.80/1.50	0.02/0.13
DRPA	43/47	-0.65/-1.11	-3.05/-4.46	-0.12/0.36
AZLI TID				
No DRPA	24/26	10.53/2.78	7.95/5.25	-2.34/-0.22
DRPA	45/37	6.67/2.93	9.51/3.40	-1.35/-0.42

*DRPA resistance to at least 1 antibiotic in 2 of the 3 classes tested

110 Chronic toxicity study of lancovutide in beagle dogs

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Lancovutide (Moli1901) interacts with plasma and organelle membranes, where it activates an alternative chloride channel by elevating intracellular calcium. Ca-activated alternative Cl-efflux in the lower airways of CF patients may compensate for reduced or absent CFTR function.

In this ICH/GLP conforming chronic toxicity study, beagle dogs received daily inhalations of lancovutide at 0, 70, 140, or 210 µg/kg during 39 weeks (4m/4f per group). Additional 2 males and 2 females of the control and high dose group were assigned for an 8 week recovery period post treatment. All animals survived to the end of the treatment or recovery periods and no clinical signs attributable to lancovutide were observed. No treatment-related ophthalmoscopic changes or changes of respiratory function parameters were observed. An increased incidence of ventricular premature complexes was seen in high dose animals during week 1 of treatment only, whereas no further abnormalities were observed at later stages. There were no effects on hematology, clinical biochemistry, urinalysis, organ weights or macroscopic findings considered to be related to lancovutide.

Minimal to moderate histiocytosis at the paracortex in the tracheobronchial lymph node was recorded at all dose groups. In addition, minimal to slight accumulation of histiocytes at the septum in the lung was recorded in middle and high dose animals. Both findings persisted during the recovery period in high dose animals. In the absence of any related inflammatory or degenerative lesion, the observed alterations were unlikely to be of adverse nature. All other microscopic findings were within the normal range.

The NOAEL in beagle dogs was estimated to be 140 µg/kg/day, representing app. 30–50 times the maximum daily dose currently used in late Phase II clinical trials. Supported by: AOP Orphan Pharmaceuticals AG, Vienna, Austria.